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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,997	SALBAUM, J. MICHAEL	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-10, 11-15 and 20-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/23/04, is acknowledged.

2. Claims 1-42 are pending.

3. Claims 1-8 and 16-19 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 9-10, 11-15 and 20-42 are under examination as they read on an isolated nucleic acid molecule of SEQ ID NO: 1 encoding Nope polypeptide of SEQ ID NO: 2 and SEQ ID NOs: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 and oligonucleotides 300-325, 325-350 and 300-350 as the species.

5. In view of the amendment filed on 6/23/04, only the following rejections are remained.

6. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

7. Claims 9-10, 11-15 and 20-42 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the same reasons set forth in the previous Office Action mailed 12/23/03.

Applicant's arguments, filed 6/23/04, have been fully considered, but have not been found convincing.

Applicant submits that the specification teaches a specific, substantial and credible utility. Analysis of the Nope sequence revealed that the protein encoded by the Nope nucleic acid sequence contains four immunoglobulin domains and five fibronectin-type domains, has structural similarity to DCC, Punc and NCAM, and most closely resembles cell adhesion molecules (page 46, lines 8-17). The specification further teaches the function of these structurally related proteins as axonal guidance receptors (page 49, line 22, to page 50, line 7). The specification also teaches the developmental expression of Nope, including its expression in cells of the nervous system (Example 11, pages 46-48, in particular page 47, line 27, to page 48, line 16). Therefore, Applicant disagrees with the assertion in the Office Action on page 2 that the specification does not disclose the biological role of the polynucleotide sequence or it significance. Applicant submits that the specification provides an explicit teaching of a specific, substantial and credible utility of the Nope polynucleotide in that it encodes a protein expressed in the nervous system and that functions as an axonal guidance receptor.

However, Applicant has not provided evidence to demonstrate that Nope polynucleotides and polypeptides of the instant specification have a specific and substantial asserted utility or a well

established utility. Mere expression of Nope polynucleotides in ventricular zone in the brain, hippocampus, the piriform cortex, thalamic nuclei, and foliae of the cerebellum does not mean that the polynucleotide is an appropriate target to regulate the development of the nervous system and related biological functions(see page 3, line 3-6 of the specification). Brain, hippocampus, the piriform cortex, thalamic nuclei, and foliae of the cerebellum can express many polypeptides, such as constitutively expressed polypeptides, which are not appropriate targets. Furthermore, Applicant asserts that the Nope polynuleotide are structural similarity to DCC, Punc and NCAM, and most closely resembles cell adhesion molecules. However, since the specification does not disclose any methods or working examples that demonstrate the Nope polynucleotide of the instant application exhibit similar activities of other immunoglobulin family and fibronectin-type proteins, the skilled artisan would not be able to categorize the polynucleotide and polypeptide of the instant application as a cell adhesion molecule.

Applicant further submits that the specification teaches that the Nope gene maps to markers on chromosome 15 that are linked to Bardet-Biedl syndrome 4 (page 57, lines 4-9. Applicant concluded that the specification additionally teaches the utility of the claimed Nope encoding nucleic acids as a chromosome marker for this devastating disease associated with mental retardation. Applicant submits that the Nope polynucleotide map to a specific chromosome location on chromosome 15. Applicant concludes that the specification teaches a specific DNA target, which can function as a chromosome marker associated with BBS4.

However, the specification on page 57, lines 4-14 and page 38, lines 7-20, discloses that the 3`-untranslated region of the Nope gene *showed sequence homology* to two human STS markers, WI-18508 an WI-16786. Both markers have been mapped close to a locus on a chromosome 15 which is linked to Bardet-Biedl syndrome 4. The specification further disclosed that considering that mental retardation is part of Bardet-Biedl syndrome, it was intriguing to detect Nope gene expression in the adult hippocampus, and area of the brain associated with cognitive functions such as learning and memory. Therefore, it is possible that the Nope gene plays a role in related human disorders. However, the specification dose not teach that Nope gene maps to markers on chromosome 15, but rather show sequence homology to STS markers that mapped close to a locus on a chromosome 15. Based on sequence homology and that Nope gene expressed in adult hippocampus, applicant concluded that Nope gene maps to markers on chromosome 15 that linked to BBS4. Applicant presented no evidence that Nope gene is a marker for any chromosome. No mapping shows that Nope gene is located on human chromosome 15q and lies within the BBS4. Furthermore, while WI-18508 is mapped to q22.31, WI-16786 is mapped to q22.32 and BBS4 mapped to q22.32 on chromosome 15, any genetic element on chromosome 15q can be use as chromosome 15 markers that are linked to BBS4 and therefore, applicant's utility is not specific. Actually, most of the other markers are closer (which provide less recombination frequency) to the locus on chromosome 15q which is linked to BBS4. Any genetic element (locus, allele, DNA sequence or chromosome feature) which can be readily detected by phenotype, cytological or molecular techniques, and used to follow a chromosome or chromosomal segment during genetic analysis can be used as chromosome marker. Therefore, the claimed utility as a chromosome marker that are linked to BBS4 is not specific.

Applicant submits that the claimed Nope encoding nucleic acids, the specification teaches that the nucleic acid encodes a polypeptide having four immunoglobulin domains and five fibronectin-type domains, both of which are well characterized structural domains (page 46, lines 8-17). Further, Applicant submits that the specification teaches that Nope is related to axonal guidance receptors (page 49, line 22, to page 50, line 3). Furthermore, the specification teaches that Nope is expressed in the nervous system, consistent with its role in axonal guidance. Applicant contends that in contrast to the comments in Attwood and Skolnick et al. related to making "functional assignments "merely on the basis of some degree of similarity between sequences," the claimed nucleic acids encoding Nope are correlated in the specification with well known structural motifs, proteins well known function and tissue expression consistent well known function.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases (Attwood and Skolnick et al). Further, it is recognized that protein functions are highly dependent on their tertiary structures. The folding properties of proteins are still some what of a mystery with much left to be learned. Therefore, even with high homology between primary structures of proteins their functions, small differences in amino acid sequences structures may affect the proteins' folding properties for some classes of protein and thus their functions may not be conserved. The sequence, structure and function of proteins can be combined in different ways. There are proteins with very different sequence fold similarly and perform similar function, proteins with very similar sequence fold up differently, or proteins with very similar functions but still very different structure. Certain positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. The rejection sets forth that among related polypeptides, structural similarity is not predictive of functional similarity. Therefore, functional relatedness is not credible in the face of evidence in the art that structurally related polypeptides are frequently dissimilar functionally.

Regarding Metzler et al Applicant assert that Metzler et al corroborates Applicant's position that conserved domains are predictive of analogous function. Applicant contends that mutation of a conserved domain reduces binding activity is consistent with the conservation of the domain being important for ligand binding, and the conservation of domains as found in homologous proteins is the basis for why homology analysis is one important criteria that can be use to predict the function of a homologous protein.

Metzler et al reference demonstrate that event a single amino acid substitution will often dramatically affect the biological activity and characteristic of a protein. It is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional

structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved. Therefore, a 45% sequence identity (to Punc) in the region ranging from the beginning of the second Ig domain throughout the first FnIII repeat would provide sequence domains that have distinct biological activities.

Applicant argues that the utility of the claimed polynucleotide can be imputed based on the relationship between the Punc, Neogenin, DCC. Applicant states that the guidelines further indicate that [when a class of proteins is defined such that the members share a specific, substantial and credible utility the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial and credible utility to the assigned protein.]

However, without some common biological activity for the family members, a new member would not have a specific, or substantial utility when relying only on the fact that it has structural similarity to the other family members. While Applicant's Nope gene has 45% similarity to Punc, however Marg *et al* in J Cell Biology (145:865-876, 1999) show that despite the similarities between neurotractin-L form and neurotractin-S form proteins, wherein the S form sequence is completely contained within the L-form sequence (i.e. 100% sequence identical to L-form), there are significant differences in their function. Only the L-form has been found to mediate adhesion and neurite initiation of telencephalic neurons (see entire document in particular). Furthermore, neurotractin-L form binds stronger to CEPU-1 or LAMP than the S-form (see page 874). The members of the family have different biological activities, but there is no evidence that the claimed compounds would share any one of those different activities. That is, no activity is known to be common to all members of Ig-like protein. This case is analogous to Brenner V. Manson. Since some Ig members are functional and some are non functional, therefore, a person of ordinary skill in the art could not impute utility based on a substantial likelihood. Further, one ordinary skilled in the art at the time the invention was made could not determine whether the expression of Nope would function as axonal guidance receptor and mediate adhesion. One of ordinary skilled in the art would be able to use such information for research to identify and characterize the encoded proteins of the invention. Such research has been determined by the courts to be a utility, which, alone, does not support patentability.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 9-10, 11-15 and 20-42 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Further, the specification does not provide sufficient enablement for how to make any nucleic acid molecule encoding a Nope polypeptide of SEQ ID NO: 2 or "modification" of the encoding nucleic acid sequence or a modification of SEQ ID NO:1 in claims 9-10; the isolated nucleic acid molecule "comprising" nucleotide sequence SEQ ID NOs: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23 in claims 11. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 12/23/2003.

10. Claims 9-10 and 14 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 12/23/2003.

Applicant's arguments, filed 6/23/04, have been fully considered, but have not been found convincing.

Applicant argues that with regard to the term "modification," the specification teaches that a modification of a nucleic acid can include one or several nucleotide additions, deletions or substitutions with respect to a reference sequence, including a substantially the same nucleotide sequence that can hybridize under moderately stringent or higher stringency conditions (page 9, lines 16-30). The specification also teaches various stringency conditions (page 24, line 15, to page 25, line 18). Therefore, Applicant respectfully submits that the specification provided sufficient description and guidance to enable the claimed nucleic acid molecules and modifications thereof.

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the nucleic acid which are tolerant to change (e.g. such as by nucleic acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Due to the large quantity of experimentation necessary to obtain such "modification" of Nope polynucleotide variants, to generate the infinite number of derivatives recited in the claims and to determine the specific activity of the infinite variants, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art

which establishes that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
July 27, 2004

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